

Effect of growth hormone on height, weight, and body composition in Prader-Willi syndrome

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Abstract

Aims—To evaluate the effect of the administration of growth hormone on stature, body weight, and body composition in children aged between 4 and 10 years with Prader-Willi syndrome.

Methods—Height, weight, and skinfold thickness were recorded in 25 children using standard anthropometric techniques at recruitment, and six months later, shortly before the start of daily subcutaneous injections of growth hormone. Body composition was assessed via a measurement of total body water using stable isotopes. Measurements were repeated at the end of the six months of growth hormone administration. Measurements of height, weight, and skinfold thickness were expressed as standard deviation scores (SDSs).

Results—There was a significant reduction in the percentage of body fat after growth hormone treatment; height velocity doubled during treatment; body weight did not change significantly when expressed as an SDS. Skinfold thickness at both the triceps and subscapular site decreased in absolute terms and when expressed as an SDS.

Conclusions—These results indicate sufficient potential benefit to justify a more prolonged trial of growth hormone treatment and an exploration of different dosage regimens in children with Prader-Willi syndrome.

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has received little attention in published work, with only a few reports, and some of these single case histories.⁷⁻¹⁰ With the ready availability of biosynthetic growth hormone, however, there is increased pressure on clinicians to prescribe growth hormone for children with Prader-Willi syndrome, despite the lack of evidence of its efficacy. The high cost of treatment with growth hormone and the possibility of side effects also influence decisions about the prescription of growth hormone in these patients. Potential benefits considered by clinicians are most likely to be changes in stature, weight, and body composition after growth hormone treatment. We therefore investigated the effect of growth hormone administration on body size and body composition in a group of children with Prader-Willi syndrome.

Subjects and methods

Twenty five children (18 boys, seven girls) were recruited with the assistance of the Prader-Willi Association (UK) and consultant paediatricians throughout the UK. Inclusion criteria were that the boys were aged between 4 and 10 years and the girls between 4 and 9 years. These ranges were chosen to reduce the chances of pubertal changes influencing the interpretation of alterations that might occur in body size and body composition. Diagnosis of Prader-Willi syndrome must have been based on either a reported deletion of chromosome 15 in the 1-13 band or the child satisfying other accepted diagnostic criteria.¹¹

Ethical approval for the study was obtained from the Dunn Nutrition Unit Medical Research Council ethical committee and from the health authority of each subject. The parents of the children gave written informed consent for the study.

After initial recruitment (time 0) and assessment, a control period of six months started. After this time (time 6), further assessments of body size and body composition were made. There then followed a further period of six months during which the child received daily subcutaneous injections of growth hormone (Humatrope; Lilly, Basingstoke, Hants, UK) at a dose of 20 IU/m²/week after which (time 12) body size and body composition were assessed for a final time. The following measurements were made at times 0, 6, and 12.

ANTHROPOMETRY

Body weight, stature, and skinfold thicknesses were measured. Body weight was recorded to the nearest 100 g using a Schoele digital scale with the child wearing minimal clothing. Height was measured to the last completed millimetre using a Karmimeter (Raven Equipment).

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The Prader-Willi syndrome is characterised by a number of features that include hypotonia beginning in the prenatal period, hypogonadism, short stature, mental retardation of a variable degree, hyperphagia, and obesity.¹ The obesity usually develops within the first four years of life and, as adolescents and young adults, weight for height can exceed 200% of normal.² A number of these features, namely, short stature, obesity, and hypotonia, might be affected by administered exogenous growth hormone. Indeed, the lipolytic and anabolic effects of growth hormone on body composition may be more beneficial to children with Prader-Willi syndrome than the more obvious potential for improving linear growth. There have been contradictory reports about the endogenous production of growth hormone secretion in the syndrome,³⁻⁵ but the more recent work suggests that neurosecretory abnormalities may be a common feature of Prader-Willi syndrome.⁶

The effect of growth hormone administration in children with Prader-Willi syndrome

Table 1 Physical characteristics of 25 children with Prader-Willi syndrome

Physical characteristic	Time 0	Time 6	Time 12
Age (years)	6.62 (1.48)	7.08 (1.47)	7.6 (1.47)
Height (cm)	109.6 (10.9)	112.1 (11.1)	117.8 (10.9)
Height (SDS)	-1.87 (1.25)	-1.90 (1.28)	-1.33 (1.24)
Weight (kg)	26.2 (11.8)	27.8 (13.0)	29.7 (14.1)
Weight (SDS)	0.43 (1.8)	0.44 (1.8)	0.49 (1.73)
Triceps skinfold (mm)	17.2 (4.7)	17.6 (4.0)	14.9 (6.2)
Triceps skinfold (SDS)	2.01 (0.81)	1.98 (0.65)	1.27 (1.25)
Subscapular skinfold (mm)	17.8 (7.6)	16.4 (7.6)	13.8 (7.6)
Subscapular skinfold (SDS)	2.33 (0.75)	2.02 (0.72)	1.52 (1.12)
% Fat	36.7 (10.4)	40.6 (11.9)	32.5 (12.5)
% Fat free mass	63.3 (10.4)	59.4 (11.9)	67.5 (12.5)

Time 0; at time of recruitment; time 6; six months after recruitment (before treatment started); time 12, after 6 months of growth hormone treatment (12 months after recruitment).

Values are mean (SD).

SDS, standard deviation score.

Skinfold thicknesses were measured (when possible) at the triceps and subscapular sites using Holtain callipers (Holtain, Crymch, Dyfed, UK).

BODY COMPOSITION

The assessment of body composition used the measurement of total body water using the stable isotope ^2H in the form of water ($^2\text{H}_2\text{O}$). A dose of 0.05 g/kg body weight was administered by mouth. The dose was given from a standard 125 ml bottle via a drinking straw. In all instances the dose consumed was measured to two decimal places of a gram. A single urine sample was collected before the administration of the dose and further samples collected between four and six hours later, and then daily for 10 days. The isotopic enrichment of the urine samples was measured using isotope ratio mass spectrometry (Aqua-Sira; VG Isotech, Cheshire, UK). Total body water was calculated using a modification of the equation described by Halliday and Miller¹²:

$$N = \frac{TA}{a} \times \frac{E_a - E_t}{E_s - E_p}$$

where N is total body water (g), A is the dose of isotope given (g), a is the weight (g) of a portion of the dose retained for mass spectrometer analysis, T is the weight of the tap water in which the portion (a) is diluted, E_a is the enrichment of the portion, E_t is the enrichment of tap water, E_s is the antilog of the intercept of the regression line of the logarithm of the post-dose enrichment against time, and E_p is the enrichment of the predose urine sample. All enrichments are expressed as delta units relative to a local standard. The dilution space was reduced by 4% to correct for the exchange of isotope with non-aqueous hydrogen.¹³

Fat free mass was calculated from body water by using reference values¹⁴ for the water content of the fat free mass. Fat mass was calculated as body weight minus fat free mass.

STATISTICAL ANALYSIS

Measurements of body weight and stature were converted to standard deviation scores (SDSs) for each child using the published UK growth standards,¹⁵ thus adjusting for age and sex simultaneously. Skinfold thicknesses at the triceps and subscapular sites were also converted to SDSs.¹⁶ Multiple regression analysis was used to assess which variables influenced the magni-

tude of the change in stature and body composition after the growth hormone treatment.

Results

Table 1 shows some physical characteristics of the subjects at recruitment, 6 months, and 12 months. Average stature at recruitment was close to the third centile (SDS -1.87), but the average body weight was close to the 67th centile (SDS +0.43). The mean triceps and subscapular skinfold thicknesses were above the 97th centile. The mean percentage body fat was high at 36.7%.

The stable isotope assessment of body composition showed that the mean percentage of body fat increased from 36.7% to 40.6% between time 0 and 6 months. There was no significant difference in any of the age and sex adjusted variables (that is, those expressed as SDSs) or in the percentage body fat between time 0 and 6 months.

After six months of daily subcutaneous injections of growth hormone the average stature had increased by 5.7 cm, which was more than double the growth velocity of the previous six months, so that the mean height SDS at the end of the treatment period was -1.33. The change in stature while receiving growth hormone treatment varied considerably within the cohort, with the range extending from 3.2 to 7.7 cm (a coefficient of variation of 19%). Weight and weight SDS had increased by 1.9 kg and 0.05 respectively.

It was not possible to record skinfold thickness on seven occasions. This was because the skinfold thickness was greater than the calliper's jaw aperture (40 mm). Four of the missing skinfold measurements were at recruitment, the remaining three at six months into the study. These missing data were less than 5% of the available data and as such are not expected to influence the results.

Both skinfold thicknesses had reduced at both sites, in absolute terms and as SDSs. The percentage of body fat had decreased on average by 8.1 percentage points to 32.5%. The change in body fat also varied between subjects; these ranged from a gain in fat of 9.3 percentage points to a loss of 19.2 percentage points at the other extreme. A paired *t* test for differences in percentage body fat at 6 months and 12 months was significant ($t = 2.32$; $p < 0.025$).

The mean decrease in percentage body fat was accompanied by a mean increase in percentage fat free mass during the six months of growth hormone treatment from 59.4 to 67.5%. This change was also statistically significant ($t = 2.32$; $p < 0.025$).

Between time 6 and time 12 the mean change in height SDS was 0.560, which reflects an improvement in growth velocity. A paired *t* test of these SDS changes between time 0 and time 6, and time 6 and time 12 was highly significant ($t = 10.59$; $p < 0.0001$).

Tables 2 and 3 show the results of the multiple regression analysis to determine the influencing factors on change in height SDS and percentage body fat. Table 2 shows that the most significant factor predicting the change in height SDS was

Table 2 Regression analysis with the change in height SDS as the dependent variable and age, % fat at 6 months, height and weight SDS at 6 months, and sex as the independent variables

Predictor	Coefficient	t value	p value
Constant	0.74	2.81	0.01
Age	-0.07	-1.98	0.06
% fat at 6 months	0.01	1.83	0.08
Weight SDS at 6 months	-0.11	1.65	0.12
Height SDS at 6 months	0.05	0.58	0.57
Sex	-0.03	-0.27	0.79

Table 3 Results of regression analysis with the change in % fat as the dependent variable and age, % fat at 6 months, height and weight SDS at 6 months, and sex as the independent variables

Predictor	Coefficient	t value	p value
Constant	6.75	0.73	0.47
Age	1.02	0.82	0.43
% fat at 6 months	-0.66	-2.78	0.01
Weight SDS at 6 months	3.85	1.59	0.13
Height SDS at 6 months	-2.08	-0.75	0.46
Sex	-0.69	-0.18	0.86

the age of the child ($p = 0.06$) and the percentage body fat ($p = 0.08$) at the start of growth hormone treatment. The shortest children and those with the greatest percentage body fat showed the greatest changes.

Table 3 shows that only the percentage body fat at the initiation of growth hormone treatment significantly predicted the response in body composition to growth hormone treatment ($p < 0.01$). Again, the children with the largest percentage body fat showed the greatest changes.

Discussion

After six months of treatment with daily subcutaneous injections of growth hormone in 25 children with Prader-Willi syndrome, there were significant improvements in linear growth and body composition. The mean increment in stature during the six months of treatment was 5.7 cm (range 3.2–7.7 cm), a major improvement in linear growth. This does not necessarily indicate that final adult stature would be greater if growth hormone treatment was continued, final height might simply be reached more quickly.

In the current treatment of Prader-Willi syndrome a major goal is the control of excessive weight gain, and specifically excessive fat gain. Thus the fact that the mean body weight, in absolute terms and when expressed as SDSs, increased during the course of the study may be a disappointment. However, this does not take into account the major changes in body composition that occurred during growth hormone treatment.

The normal changes in body fat as a percentage of body weight between the ages of 4 and 10 years in normal children are relatively simple. In both sexes there is a gradual decrease in the percentage body fat from about 17% of body weight at 4 years of age to a nadir at around 7 years of age, with levels of approximately 12% in boys and 16% in girls. A gradual increase then occurs in both sexes to reach values of 18% in boys and 19% in girls at 10 years. The mean percentage body fat in the children

with Prader-Willi syndrome of 36.7% at recruitment is considerably above the expected values. During the six months of pretreatment observation the mean value increased by nearly 4 percentage points, again a greater than expected gain. During growth hormone treatment 21 of the 25 children showed a reduction in the percentage body fat. This was accompanied by a gain, on average, of 4 kg in fat free mass. Body weight increased due to the fact that the densities of fat free mass and fat mass are not the same. The changes in body composition are significant and beneficial, and show the need for body composition assessment in the evaluation of the effects of growth hormone treatment, rather than a simple assessment of changes in body weight.

In conclusion, this study has shown that in prepubertal children with Prader-Willi syndrome treatment with growth hormone at a dosage of 20 IU/m²/week for six months produced a substantial increase in height velocity and considerable changes in body composition, with decreased fat and increased fat free mass, these changes relating to the height and fat mass at the start of the study. It is of interest that several parents spontaneously volunteered that their children were more active and energetic when receiving growth hormone. These results seem to indicate sufficient potential benefit to justify a more prolonged trial of growth hormone treatment and exploration of different dosage regimens.

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